REMARKS

Claims 105, 106, 108, 124, 125, 127-130, 132-135, 165 and 166 remain pending after response.

Allowable Subject Matter

Applicants acknowledge with appreciation the indication of allowable subject matter of claims 97, 100, 137, 138, 150 and 151. These claims are cancelled and limitations thereof incorporated into the pending claims.

Claim Amendments

By this amendment, claims 89-104 and 137-164 are cancelled. New claims 165-166 are added. Claims 105, 106, 108, 124 and 135 are amended. No new matter is added by this amendment.

Applicant remains of the view that the cited prior art references, including newly-cited **EP0511895A1** and **Maramag et al**, do not anticipate, render obvious, or otherwise prejudice the claims currently pending.

However, in an attempt to expedite favorable consideration of the pending claims, applicant limits the claims to methods of treating neoplastic disease in a human or animal patient which comprise administering to the patient an anti-neoplastic effective amount of a composition comprising **as the sole pharmaceutically active components**:

(a) copper ***gluconate*** or copper ***orotate***;

(b) ***sodium*** salicylate;

(c) vitamin C;

(d) manganese ***gluconate*** or manganese ***orotate***; and

optionally one or more of:

(e) iron ***gluconate*** or iron ***orotate***;

(f) ***sublimed*** sulphur; and

(g) zinc ***gluconate*** or zinc ***orotate***.

The above claim amendments are now believed to place the claims in condition for allowance. For instance, the Examiner notes at page 3 of the Action that "The difference between the prior art and the claimed invention is that the prior art does not expressly disclose the use of copper orotate, manganese orotate, iron orotate, sodium salicylate, a source of assimilable sulphur, and vitamin C."

The Examiner also notes at page 7 of the Action, in discussing the merits of the comparative data made of record by applicant, that "these declarations and that the data in the specification only show that sodium salicylate, ascorbic acid, copper gluconate and/or orotate and manganese gluconate and/or orotate are effective as anti-tumor agents."

In view of the above claim amendments, as well as the above statements of the Examiner in the outstanding Action, and the Examiner's indication that the subject matter of cancelled claims 97, 100, 137, 138, 150 and 151 is allowable, the amended claims should be found to be allowable as patentably distinguishing over the cited prior art.

Rejection under 35 USC 103(a)

Claims 89-96, 98, 99, 101, 102, 104-106, 108, 124, 125, 127-130, 132-135, 139-147, 149 and 152-164 stand rejected under 35 USC 103(a) as being unpatentable over **Jackson** in view of

Riley et al, Klampfer et al, Wawretschek et al, Herschler '421, Herschler '039 , DE 2457424, EP 0511895, Maramag et al, and **Memnon et al**. This rejection is respectfully traversed.

The claimed method is neither disclosed nor suggested by the cited prior art, as is apparent from the following discussion of the deficiencies of the prior art relied upon by the Examiner.

The pending claims are based on applicant's surprising discovery that a composition containing at least these four components (and optionally, but not necessarily, others) is effective in combating neoplastic disease. The data provided in the application (cf. Examples 11 to 18) clearly demonstrates the striking effects of compositions comprising said four components in treating cancer. In each of said studies, the compositions in accordance with the invention (consisting of sodium salicylate, vitamin C, manganese orotate, and copper gluconate or orotate) were effective in inhibiting, halting, or even reversing tumour growth. Reference is made, in particular to Examples 11 and 13 and related Tables 1 and 2 of the application, in which studies the mice treated with the claimed compositions had significant reductions in tumour mass and increases in life expectancy as compared to the control mice.

As further evidence of the efficacy of the claimed compositions in treating neoplastic disease, applicant previously submitted reports of two further animal studies investigating the anti-neoplastic effects of a composition (referred to as CV247) in accordance with the invention (consisting of sodium salicylate, vitamin C, manganese gluconate, and copper gluconate). Again, this data demonstrates that animals treated with the compositions of the present invention show a clear reduction in tumour mass/volume as compared to the control animals untreated with the compositions. Moreover, this data also supports the teaching of the present application that it

is the claimed combination of components that leads to the particular efficacy of the claimed compositions in treating cancer. In particular, the compositions comprising all the claimed components (CV247) had demonstrably greater benefits than sodium salicylate alone or in combination with vitamin C.

Applicant maintains that the presently claimed method is neither disclosed nor suggested by the prior art of record, for the following reasons.

With reference to the Examiner's comments at page 7 of the Office Action, the claims as amended are now limited to those species (i.e. sodium salicylate, vitamin C, and gluconate or orotate salts of copper and manganese) for which data in the specification and subsequently filed Section 132 declarations have been provided. Moreover, all claims now require that the composition comprises these species (optionally in combination with sublimed sulphur, zinc gluconate/orotate, and/or iron gluconate/orotate) as the sole pharmaceutically active components, which further distinguishes the claimed subject matter from the prior art.

The data of record demonstrates that the administration of the recited compositions is effective in combating cancer, and that it is the recited combination of components that leads to the particular efficacy of the compositions in treating cancer. As regards the former point, reference is made in particular to Examples 11 and 13 and related Tables 1 and 2 of the present application, showing that the mice treated with the claimed composition had significant reductions in tumour mass and increases in life expectancy as compared to the control mice, and to the second of the Section 132 declarations (Declaration #2), similarly demonstrating a clear reduction in tumour mass/volume where the claimed composition is used. As regards the latter point, reference is made to the first of the Section 132 declarations (Declaration #1), showing that treatment with 10ml/kg of CV247 (equating to administration of 35mg/kg of sodium

salicylate, 40mg/kg of vitamin C, and 2mg/kg of each of copper gluconate and manganese gluconate) resulted in a greater reduction in tumor mass and higher levels of intra-tumoral necrosis than the same amount of sodium salicylate, sodium salicylate + vitamin C, sodium salicylate + vitamin C + copper gluconate, or sodium salicylate + vitamin C + manganese gluconate on their own.

Notwithstanding the above, however, the Examiner maintains (also on page 7 of the Office Action) that the prior art discloses a composition containing copper gluconate, manganese gluconate, and ascorbic acid that is effective against cancer; that the prior art also suggests sodium salicylate as being effective against cancer; and that it would therefore have been obvious to one of ordinary skill to combine these components to arrive at a method as claimed. Applicant disagrees with the Examiner's position.

The Examiner relies on an untranslated copy of **EP0511895A1** in support of the rejection. Applicant accordingly submits herewith a translation of **EP0511895A1,** originally cited in French. Based on this translation, and on applicant's understanding of the original French text, the teachings of this document are summarised below.

The document teaches a sanogenic (i.e. health promoting) composition that is stated to have an anti-cancer action. The asserted anti-cancer action seems to be primarily a preventative action, although there is a suggestion of a curative anti-cancer effect in the case of nascent neoplasias (*cf.* page 2, lines 9-12 of the original text, corresponding to page 1 third paragraph of the enclosed translation). No data or other evidence of any sort is provided to support the asserted preventative or anti-cancer effect. The composition itself contains 30 components (see the list on page 3 of the original text and page 3 of the translation). While this list does include ascorbic acid, manganese gluconate, and copper gluconate, the components indicated as

providing an anti-cancer affect are choline, methionine, ascorbic acid, and molybdate (page 2, lines 50-56 of the original text, page 2 last paragraph of the translation). Finally, there is no suggestion in this document of the inclusion of sodium salicylate or any other derivative or salt of salicylic acid. In fact, it is stated the components of the composition should be such as exhibit adverse effects, if any, only if consumed in amounts several times higher than the amounts usually consumed (page 2, lines 37-39 of the original text, corresponding to page 2 second paragraph of the enclosed translation).

Maramag suggests the use vitamin C as a cancer treatment, and provides *in-vitro* data with respect to the effects of vitamin C on prostate cancer cells. There is no teaching in this document regarding, manganese, copper, or sodium salicylate or its salts or derivatives, either on their own or in combination with vitamin C.

The other cited art, having been previously made of record, has of course been extensively discussed in applicants' earlier responses (in particular in the response of March 24, 2008), and for the sake of conciseness, such prior analysis is not repeated in full here, but otherwise incorporated by reference, and the Examiner's attention is directed thereto. Nonetheless, the following summary of such prior distinguishing comments is provided for the Examiner's consideration.

Jackson discloses a dietary supplement for supplementing the micronutrient and phytochemical needs of a woman at various stages during her life cycle to prevent or reduce the risk of (not treat) a number of conditions, including some cancers. The supplement is a composition comprising copper, vitamin C, manganese and twelve other components (including iron and zinc, but not salicylic acid or any salt or derivative thereof) in admixture with a biologically acceptable carrier (see column 2, line 34 to column 3, line 21)

Riley discloses a modular system of multivitamin and mineral supplementation to replace micronutrients lost as a result of lifestyle factors and inadequate diet thereby improving public health by insuring adequate intake of micronutrients needed for disease prevention and for reducing the risk of chronic diseases such as cancer (amongst others). Modules 4, 5 and 6 of **Riley** contain aspirin, with Modules 5 and 6 further including copper, vitamin C, and manganese, together with 23 other components (including iron and zinc). Aspirin is used in **Riley** primarily for its antiplatelet aggregating capacity, so as to reduce the risk of coronary heart disease. There is also suggestion of the use of bioequivalents of asprin, but as is well known (and indeed as is evidenced by the previously submitted extract from Martindale) it is well known that salicylic acid and alkali and alkaline earth metal salts thereof do not share the antiplatelet aggregating capacity of asprin. As such there is no suggestion in **Riley** to use salicylic acid, or any alkali or alkaline earth metal salt thereof, in the modular systems described therein.

Klamfer teaches that sodium salicylate (Na-Sal) can induce apoptosis in several myeloid leukaemia cell lines tested. It also teaches that, at sub-lethal concentrations, Na-Sal potentiates the known apoptotic effects of growth factor withdrawal or treatment with daunorubicin. No *in vivo* data is presented, but on the basis of the aforementioned *in vitro* data the authors propose that Na-Sal may have therapeutic potential for the treatment of human leukaemia. The document also refers to the previous papers investigating the use nonsteroidal anti-inflammatory agents (NSAIA) in general as chemo*preventative* agents (i.e. as agents for *preventing*, rather than *treating*, cancer). There is no teaching in this document regarding vitamin C, manganese, or copper, either on their own or in combination with sodium salicylate.

Wawretschek discloses a means of reinforcing the pharmacological action of medicaments which exhibit an affinity for linking with blood proteins *in-vivo* and *in-vitro*.

Orotic acid and/or a physiologically tolerable orotic acid salt are used to provide a controlled increase of that portion of the drug to be used which is not bonded to the serum albumen. In Example 5 the analgesic efficacy of sodium salicylate is examined, both alone and in a binary composition with choline orotate. There is no disclosure of the use of copper, manganese, or vitamin C, nor is there any teaching relating to the treatment neoplastic disease.

DE 2457424 teaches that zinc orotate is effective against cancer. There is no teaching regarding any of sodium salicylate, vitamin C, copper, or manganese.

Herschler '421 discloses the use of methylsulphonylmethane ("MSM") to ameliorate the symptoms of stress (specifically gastrointestinal upset, inflammation of the mucous membranes and allergic reactions). In one example MSM is administered with and without ascorbic acid (Vitamin C) to treat mucous membrane inflammation at least partly associated with lung tumours. Treatment (both with and without Vitamin C) appears to have alleviated inflammation, and caused significant regression of tumour mass. There is no teaching in this document regarding copper, manganese, or salicylic acid or an alkali or alkaline earth metal salt thereof.

Herschler '039 discloses that MSM is an assimilable form of sulphur. It also discloses that supplementation of diet with 2 wt % MSM can inhibit DMBA-induced mammary carcinomas in rats and that supplementation of diet with 3 wt % MSM in water can protect against otherwise lethal spontaneous mouse lymphomas. As with **Herschler '421**, there is no teaching in this document regarding copper, manganese, or salicylic acid or an alkali or alkaline earth metal salt thereof.

Memnon teaches that vitamin C was effective in *in-vitro* studies in reducing cell viability of two prostate cancer human cell lines. On this basis, the authors suggest that vitamin C is an anti-cancer agent for prostate cancer cells. The document also makes reference to previous

studies describing a "protective role" of vitamin C in certain types of cancer. There is no teaching in this document regarding, manganese, copper, or sodium salicylate or its salts or derivatives.

As is apparent from the above, *there is no teaching in the cited prior art that manganese or copper has any effect, alone or in combination with any other components, in treating cancer*.

The only teaching regarding either of these two components is in documents **EP0511895A1**, **Jackson** and **Riley**. However, all of these documents, including newly cited **EP0511895A1**, are primarily concerned with dietary compositions for promoting general health, and with this in mind propose the use of compositions containing large numbers of vitamins, minerals and/or other actives.

Neither **Jackson** nor **Riley** suggests that the compositions described therein have any utility in treating cancer. Applicant maintains that it is a fallacy to suggest that one of ordinary skill in the art would consider that a teaching of a composition as having a utility in preventing cancer from occurring (by promotion of general health) *per se* suggests usefulness in treating an existing cancer, nor has the Examiner provided any factual support for this as a general proposition.

EP0511895A1 does make passing reference to the composition disclosed therein as having an anti-cancer effect on nascent neoplasias, but the document provides no evidence for this. Moreover, **EP0511895A1** itself states that the components having an anti-cancer effect are choline, methionine, ascorbic acid, and molybdate – thus the teaching of this document is that manganese and copper do ***not*** contribute to any anti-cancer effect, and are administered for other reasons.

Thus, the prior art as a whole fails to provide any teaching or suggestion to administer manganese and copper as active ingredients (in combination with vitamin C and sodium salicylate) for treating cancer (as is required by the claims as presently amended).

Furthermore, the claims of the present application not only require that gluconate or orotate salts of manganese and copper are administered as active ingredients for treating cancer, they also require that these components, alongside vitamin C, sodium salicylate and the optional iron, sulphur and zinc components, are the sole active agents present in the composition administered.

In comparison, **EP0511895A1**, **Jackson** and **Riley** all expressly teach the administration of compositions comprising multitudes of other actives (that are excluded in the presently claimed methods). Thus applicant submits that, even if the skilled person were to be referred to these documents, these being the only cited documents that mention manganese or copper, it cannot realistically be held that it would have been obvious to the skilled person to attempt to treat cancer by administering a composition including manganese or copper while at the same time excluding various of the other active components that these documents teach should be present.

As regards **EP0511895A1** in particular, the skilled person would have to exclude 3 of the 4 components taught in this document as actually having an anti-cancer effect (choline, methionine, and molybdate), while including manganese and copper (despite there being no teaching regarding these having an anti-cancer effect) but also not various other vitamins and minerals. It is respectfully submitted that such steps would have been counter intuitive and run contrary to the teaching of this document, and no cogent reasons have been advanced by the

Examiner as to why it would have been obvious to the skilled person to proceed in such a manner.

As regards **Jackson** and **Riley**, these do not teach treatment of cancer at all, and administration of a composition for general dietary or health purposes does not fall within the scope of the claims of the present application. However, even if the skilled person were to have faced the different task of preparing a composition for administration for general health, again applicant cannot see how it would be obvious with this objective in mind to administer a composition containing copper and manganese, but not various of the other actives taught in these documents.

In addition, it is of course the case that neither **EP0511895A1**, **Jackson** nor **Riley** provides any teaching regarding the fourth component that must be present as an active in the presently claimed methods, namely sodium salicylate. Applicant acknowledges that other of the cited prior art documents, specifically **Klamfer**, teaches that sodium salicylate may have therapeutic potential for the treatment of human leukaemia. Equally, certain of the cited prior art documents (i.e. **Maramag**, **Memnon**, **EP0511895A1**) do teach that vitamin C may have an anti-cancer effect.

However, applicant maintains that there is no teaching in the cited art to indicate sodium salicylate and vitamin C **can be successfully combined for use in a method of treating cancer**, let alone that the combination of sodium salicylate and vitamin C (or moreover the further combination of these two components with manganese and copper) would provide the enhanced anti-cancer effect now demonstrated by the data submitted by the applicant.

Indeed, **EP0511895A1** teaches that components of the composition taught therein may exhibit adverse effects only if consumed in amounts several times higher than those usually consumed. This, of course, is not the case for NSAIAs such as sodium salicylate, which compounds present a life threatening risk in the case of significant overdoses. Thus, **EP0511895A1** in fact provides a clear teaching away from the inclusion of sodium salicylate in compositions as taught therein.

The Examiner notes (pages 6 and 7 of the Office Action) that the mere existence of hundreds or thousands of possible combinations does not make the combinations non-obvious, and that obviousness does not require absolute predictability (as to the effects of a particular combination). However, applicant submits that it is equally the case that the mere fact that a multitude of compounds are known to have a certain activity individually does not make a specific combination of compounds obvious, and that where the prior art fails to provide any indication (let alone any level of predictability) as to what the effect of a particular combination may be then this can be relevant to obviousness. In the present case, the enhanced anti-cancer effect exhibited by the claimed combination of sodium salicylate and vitamin C (and further combination of these components with manganese and copper) clearly constitutes an unexpected yet highly desirable result. The fact that these combinations had not previously been tested and the enhanced anti-cancer effect discovered does, it is submitted, therefore provide persuasive evidence that the use of the claimed combination of components to treat cancer was in reality not obvious.

These combined teachings, as outlined above, thus fall far short of disclosing or suggesting a method as presently claimed. Much of the art cited *does not refer to cancer treatment at all*, while such art which does refer to cancer treatment refers only to the possible

potential use of certain compounds in singly and isolation (or else in combination with compounds other than those claimed). There is no teaching in the art as a whole regarding a combination of manganese, copper, vitamin C and sodium salicylate (or salicylic acid or other alkali or alkaline earth metal salts thereof) as a treatment for cancer, nor is there any obvious reason why one of ordinary skill in the art, on reading the above cited documents (not to mention the multitude of other prior art documents relating to possible cancer treatments) would have suddenly decided to investigate or adopt such a combination as a treatment for cancer.

In particular, the cited art provides no indication or suggestion of the additive benefits of the claimed combination of components in treating cancer, or of the resulting efficacy of the combination as a cancer treatment, absent which the claimed combination is but one of hundreds if not thousands of combinations which merely could but in theory have been investigated.

For example, based on the teaching of **Klamfer**, one skilled in the art might have been motivated to investigate further the use of sodium salicylate, on its own or in combination with daunorubicin, as a treatment for cancer. Alternatively, based on **Memnon**, one skilled in the art might have been motivated to investigate further the use of vitamin C on its own.

However, there is no reason why it would have been obvious to one of ordinary skill in the art to investigate a combination of sodium salicylate and vitamin C as a treatment for cancer, let alone to investigate the further combination of these compounds with copper and manganese (which are not suggested in the cited art as having any effect on cancer treatment).

There are many putative and established anti-cancer agents available, but that does not make the combination of any and all such agents obvious. There is no reason to consider, in advance, that two different anti-cancer compounds operating (according to **Klamfer** and **Memnon**) in different manners (as regards their biochemical targets) will have beneficial effects

if combined – as is illustrated by **Klamfer** itself, which considers the synergistic effects of sodium salicylate and another known anti cancer agent (daunorubicin) surprising. Indeed, it is just as possible that two anti-cancer agents could provide no additive effect, or that the two agents could have conflicting effects (thus reducing overall efficacy).

Likewise, there is even less reason to consider that adding a compound having *no known anti-cancer effect* would be beneficial, whereas adding such additional compounds could still have adverse effects on the efficacy of the composition, or other unforeseen and undesired side effects. Thus where, as in the present case, the cited art provides no teaching to suggest to one of ordinary skill in the art that a claimed combination of compounds could or should beneficially be used in combined in a claimed method of therapy, it is submitted that the claimed subject matter is not obvious.

Again, as outlined above, it is not the applicant's contention that the claimed invention is non-obvious because the claimed combination is not disclosed in a single reference, but rather that is not suggested or rendered obvious from the art as a whole. While there is no requirement that all the components have an anti-neoplastic effect so long as the composition has an anti-neoplastic effect, the relevant question is not whether the claimed components each have an anti-neoplastic effect, ***but whether it would have been obvious to one of ordinary skill in the art to administer the combined combination of components as an anti-neoplastic treatment.***

As explained above, it would not have been obvious from the art cited that even the combination of ascorbic acid and sodium salicylate (suggested individually in **Klamfer** and **Memnon** as compounds having possible utility as anti-cancer agents) would be beneficial (as compared to their use individually), let alone that other compounds having no indicated anti-neoplastic effects (copper and manganese) could or should beneficially be added.

The fact that copper and manganese are used in multinutrient compositions does not make it obvious to add them to an anti-cancer composition (or else multinutrients would be added to all anti-cancer compositions, which is clearly not the case). It is an inevitable fact that a pharmaceutical active may interact unfavourably with another active resulting in loss of efficacy or adverse side effects in one or more patient group (reference being made to any standard pharmacopoeia which, under any drug entry, will normally have sub-headings on known interactions with other actives). Thus, the standard practice when making a pharmaceutical composition is to incorporate only those components necessary to treat the condition for which it is to be administered. This minimises the risk of unforeseen side effects resulting from interaction between multiple active components, either in the population at large or in patient groups at high risk (such as pregnant women, diabetics, immunologically compromised individuals, children, and so forth). It is then left to the physician treating a patient, on diagnosing a particular patient's needs (which may or may not involve a need for both cancer treatment and dietary supplements), to determine what *separate* compositions (for treating the *separate* conditions afflicting the individual patient) can be safely and effectively prescribed or administered.

Moreover, the applicant has provided evidence demonstrating the enhanced effects in treating cancer of the claimed combination of compounds, as compared to the components individually. Such enhanced effects of the claimed combination are not obvious from the cited art nor, for the reasons set out above, would it have been "well within the skill of one of ordinary skill in the art" to arrive at the presently claimed combination of components in the expectation that the resulting combination would be effective as anti-neoplastic composition.

The rejection under 35 USC 103(a) is this without basis and should be withdrawn.

The application is now in condition for allowance. Allowance of claims directed to the generic invention is believed proper.

Payment in the amount of $490.00 is submitted herewith as payment for the requested two month extension of time.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 50-3828 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

MUNCY, GEISSLER, OLDS & LOWE PLLC

By _____
James W. Hellwege, #28,808

Muncy, Geissler, Olds & Lowe, PLLC
P.O. Box 1364
Fairfax, Virginia 22038-1364
703-621-7140

Attachment: Translation of EP 0511895